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REVIEW

A review of antibiotic safety in pregnancy—2025 update

Johny Nguyen[1] | Victoria Madonia[1] | Christopher M. Bland[2] | Kayla R. Stover[3] | Lea S. Eiland[4] | Julia Keating[1] | Madeline Lemmon[1] | P. Brandon Bookstaver[1,5] | as part of the Southeastern Research Group Endeavor (SERGE-45) research network

[1]University of South Carolina College of Pharmacy, Columbia, South Carolina, USA

[2]University of Georgia College of Pharmacy, Savannah, Georgia, USA

[3]University of Mississippi School of Pharmacy, Jackson, Mississippi, USA

[4]Auburn University Harrison College of Pharmacy, Auburn, Alabama, USA

[5]Prisma Health Richland, Department of Pharmacy, Columbia, South Carolina, USA

Correspondence
P. Brandon Bookstaver, Department of Clinical Pharmacy & Outcomes Sciences, University of South Carolina College of Pharmacy, 715 Sumter Street, Columbia, SC 29208, USA.
Email: bookstaver@cop.sc.edu

Abstract

Antibiotics constitute the majority of prescriptions for women during pregnancy. Common bacterial infections, including urinary tract infections, skin and soft tissue infections, and upper and lower respiratory tract infections, are expected in pregnancy, similar to the general public. These infections carry additional risks to both the woman and fetus; thus, antibiotics are often prescribed. Antibiotics, like other drugs, are not benign and may carry additional risks to the fetus beyond commonly encountered adverse drug events seen across most patient populations. Since 2014, 19 new antibiotics have been approved by the United States Food and Drug Administration. Additionally, in 2018, the previously held pregnancy category rating expired, and all manufacturers' labeling was updated with new narrative language reflecting safety in pregnancy, lactation, and males and females of reproductive potential. This review provides a comprehensive summary of available data and an update to the 2015 publication regarding the safe use of antibiotics in pregnancy. The primary focus of this review is on newly approved antibiotics, along with any additional published evidence on previously reviewed antibiotics. Data on lactation or antiviral or antifungal use in pregnancy are not included. Clinicians should remain updated on current available evidence and vigilant to provide safe and effective antibiotic decision-making in pregnant women.

KEYWORDS
antibiotic, antimicrobials, beta-lactams, obstetrics, pregnancy, safety, women's health

1 | INTRODUCTION

Antibiotics account for nearly 80% of all prescription medications during pregnancy, and approximately 20%–25% of women will receive an antibiotic during pregnancy.[1,2] The most common infections pregnant women encounter are urinary tract infections (UTIs), as well as infections of the genital tract, skin or soft tissues, and respiratory tract.[3] Although antibiotic use during pregnancy requires a risk-versus-benefit decision, untreated infections, such as sexually transmitted infections (STIs) or UTIs, are associated with vertical transmission to the fetus, low birth weight, preterm birth, and premature fetal membrane rupture.[4] In a global study conducted in 2020, cephalosporins and metronidazole were the most prescribed antibiotics among pregnant women.[3] Studies show that harmful exposures to antibiotics during the first trimester have the greatest chance of causing major birth defects, while exposures in the second and third

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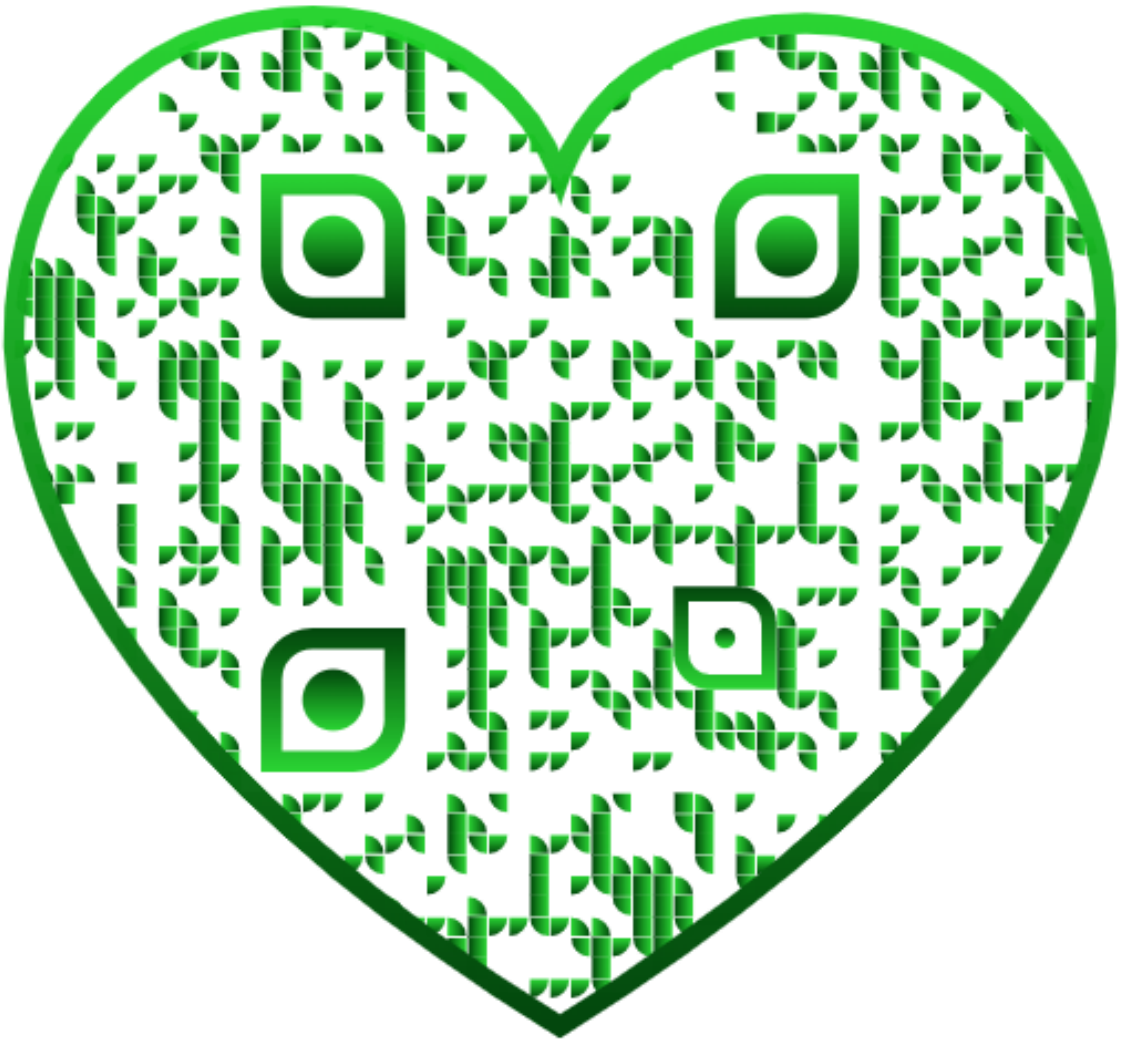

trimesters primarily cause growth problems, minor birth defects, functional defects, and learning difficulties.[5] A population-based cohort study published in 2022 found that antibiotic use during pregnancy was associated with an increased risk of preterm birth compared to infants born to women not exposed to antibiotics during pregnancy, especially in women with common comorbidities such as diabetes and hypertension (women without comorbidities: odds ratio (OR) = 1.09, 95% confidence interval (CI) [1.06–1.13]; women with comorbidities: OR = 1.32, 95% CI (1.18–1.48)).[6] Additionally, early life antibiotic exposure has been linked to alterations in the diversity of the neonate microbiome, which may be associated with conditions such as obesity and inflammatory bowel disease later in life.[7,8] Not unlike other populations, antibiotic resistance is prevalent among pregnant women with active infections and has been associated with more complicated infections, including pyelonephritis.[9,10] Stewarding antibiotics during pregnancy is essential for the protection of the woman, fetus, and ultimately newborn, and for the reduction in the development of antibiotic resistance; however, most published stewardship interventions in pregnancy focus on the assessment and management of STIs, asymptomatic bacteriuria, and penicillin allergies.[11–13]

An important development in safe use of antibiotics in pregnancy occurred in 2015 with the finalization of the United States Food and Drug Administration (FDA) Pregnancy and Lactation Labeling Rule (PLLR) dividing required narrative components in the medication label into three subsections: Pregnancy, Lactation, and Females and Males of Reproductive Potential (Table 1).[14] As of June 2018, pregnancy categories in medication labels were abandoned. Prescription drugs approved on or after June 30, 2001 were phased in gradually using the PLLR implementation plan and all medications were phased in by June 30, 2020. Based on the PLLR, medication labels are required to be updated when information is outdated.[15] The purpose of this review was to update available evidence on the safe use of systemic antimicrobials in pregnancy in a comprehensive but concise manner for clinician readers.

2 | METHODS

To update a prior review from these authors, a list of all antibiotics evaluated in the original review published in 2015, as well as all newly approved systemic antibiotics thereafter was compiled using the FDA drug approvals database.[16,17] The manufacturer's labeling for each included antibiotic was reviewed. A Medline search using the key words "[antibiotic name]" AND "pregnancy" was conducted. Two investigators cross-referenced all antibiotics with the Risk Evaluation and Mitigation Strategies (REMS) list. None of the antibiotics included in this review were found to be on the REMS list.[18] The present review focuses on articles published from June 2015, the final date of inclusion from the previous review, through November 2024.[16] Antibiotics detailed in the previous pregnancy review article are included in the present article, but only findings relating to previously unknown or unclear information are discussed in detail.[16] Nineteen antibiotics newly approved by the FDA and associated literature since the previous review are detailed in full.[17] Data on antivirals or antifungals were excluded. Safety in lactation is not discussed in this review.

3 | FINDINGS

3.1 | Aminoglycosides

Amikacin, gentamicin, streptomycin, and tobramycin are the most commonly used systemic aminoglycosides globally.[19] No new updates on these aminoglycosides in pregnancy were discovered in the literature or manufacturer's labeling. Plazomicin, approved by the FDA in 2018 for complicated UTIs, does not have any published safety data in pregnancy available. No drug-associated defects were detected in pregnant rats or rabbits given plazomicin during organogenesis.[20] Similar to other aminoglycosides, the manufacturer's labeling includes a boxed warning for the risk of fetal harm with use during pregnancy, with the highest risk associated with first trimester use.[20]

The authors of a systematic review of published literature through February 2018 identified 121 prenatal streptomycin exposures, with 18 out of the 121 (15%) exposed children exhibiting either hearing or vestibular deficits based on audiogram and caloric testing.[21] The reason for the increased risk associated with streptomycin use in pregnancy is unknown. One potential

TABLE 1 Updated medication label descriptions of pregnancy, lactation, and reproductive potential sections.[14]

Section	Description
Pregnancy	This section provides general information from a pregnancy exposure registry and the data on effects of prescribed drugs in pregnant patients It is divided into additional subsections: Risk Summary, Clinical Consideration, and Data
Lactation	This section provides information about using the drug while breastfeeding, such as the amount of drug exposed to the infant when breastfeeding and potential effects on a breastfed infant
Females and males of reproductive potential	This section provides information on the need for pregnancy testing, contraception recommendations, and information about infertility as it relates to the drug

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explanation may be due to the structural differences between the aminoglycosides; the aminocyclitol ring in streptomycin is streptidine instead of 2-deoxystreptamine.[22] Streptomycin should be avoided in the first trimester of pregnancy, as well as throughout pregnancy, unless benefits outweigh the risks. In specific multidrug-resistant infections (e.g., pyelonephritis) with no feasible alternatives available and following a careful risk assessment, a short course of aminoglycosides, aside from streptomycin, may be used in pregnancy with careful monitoring. Common risks of systemic aminoglycosides, including nephrotoxicity and ototoxicity, should be considered in the risk assessment and discussed with the patient prior to use. Although there remain few published data, the lack of significant systemic exposure expected from topical aminoglycosides (e.g., otic, ophthalmic preparations) suggests that these agents are safe during pregnancy. Table 2 provides a brief summary of pregnancy labeling and general recommendations for each antibiotic or antibiotic class.

3.2 | Beta-lactams

No new data on the safety of the historically available penicillins, cephalosporins, carbapenems, or monobactams has emerged since the prior review. These drug classes are generally considered safe for use in pregnant patients; however, caution should be taken with ceftriaxone use at term due to the risk of kernicterus in the neonate. Beta-lactams that have been approved since the previous review include ceftolozane (in combination with tazobactam), cefiderocol, ceftobiprole, pivmecillinam, and sulopenem etzadroxil (in combination with probenecid).

Ceftolozane was approved in combination with tazobactam in late 2014 for intra-abdominal infections (IAIs), hospital- or ventilator-acquired pneumonia (HAP, VAP), and complicated UTIs. It does not currently have safety data in women who are pregnant but is generally considered safe for use during pregnancy as there is no identified risk of major birth defects, miscarriage, or adverse fetal outcomes in prior cephalosporin studies.[20] Cefiderocol, approved by the FDA in 2019 for HAP, VAP, and complicated UTIs, does not yet have established safety data in patients who are pregnant. However, in animal studies, cefiderocol did not show embryo-fetal developmental toxicity in rats or mice when given at 0.9 times (rats) or 1.3 times (mice) higher exposure than the maximum recommended daily dose in humans.[20] Ceftobiprole, approved by the FDA in 2024 for bacteremia, community-acquired bacterial pneumonia (CABP), and skin and soft tissue infections (SSTIs), has no available safety data in pregnancy at the time of this review. However, in animal studies, there was no evidence of adverse developmental fetal outcomes, but there is evidence of minor maternal adverse effects such as decreased maternal body weight and appetite.[20]

Pivmecillinam is a penicillin antibiotic approved by the FDA in 2024 for the treatment of uncomplicated UTIs in women. It has been used since 1981 in France as the first-line therapy for the treatment of uncomplicated cystitis for all patients, including those who are pregnant, according to the European Association of Urology.[23] In Nordic countries, pivmecillinam has been the most commonly prescribed antibiotic for treating UTIs in pregnant women.[24] A large study using a registry of 63,659 pregnant patients in Denmark examined a cohort of 2031 patients who received pivmecillinam at any time during pregnancy.[25] Exposure to pivmecillinam during pregnancy showed an adjusted odds ratio (aOR) of 1.19, 95% CI (0.30–4.80) for the risk of stillbirth, and aOR for birth defects associated with first trimester use was 0.83, 95% CI (0.53–1.32).[25] Despite the low statistical precision, pivmecillinam should be considered safe to use during pregnancy when considering the extensive history of its usage in pregnant patients in other countries.

Sulopenem etzadroxil, approved in combination with probenecid in 2024, is an oral penem that is indicated for the treatment of uncomplicated UTIs caused by commonly encountered Enterobacterales, especially those carrying extended spectrum beta-lactamase resistance.[20] Currently, there are no reports of sulopenem etzadroxil/probenecid use in patients who are pregnant. Animal studies have shown an increased incidence of fetal malformation, specifically cleft palate, in pregnant mice exposed to 23 times the maximum recommended oral human dose (MRHD). In pregnant rats and rabbits, no oral dose was associated with fetal malformations, but higher oral doses equivalent to two times and 12 times the MRHD showed decreased maternal body weights and food consumption. In rabbits, intravenous administration of sulopenem etzadroxil decreased maternal weight gain and food consumption at all doses. Probenecid has not been associated with a risk of miscarriage, major birth deficits, or adverse maternal or fetal outcomes.[20] Given the animal data available, oral sulopenem etzadroxil/probenecid should be used in settings where the benefit of short-term exposure outweighs the risk. Overall, beta-lactam antibiotics are generally considered safe for use during pregnancy. Continued vigilance of newly approved antimicrobials without data in women who are pregnant is important.

3.3 | Beta-lactamase inhibitors (BLIs)

BLIs are rarely investigated for safety individually, but rather in combination with their beta-lactam counterpart. Established BLIs, including sulbactam and clavulanate, are generally considered safe for use in pregnancy when given in combination with ampicillin and amoxicillin, respectively. Although tazobactam, co-formulated with piperacillin or ceftolozane, is generally considered safe as well, commonly encountered beta-lactam and BLI-associated adverse events (e.g., allergic reactions, cytopenia) can still occur in pregnant individuals. A published case reported the use of piperacillin/tazobactam for cystitis in a 33-year-old pregnant patient who developed drug-associated fever, neutropenia, and thrombocytopenia, although this was not considered teratogenic.[26] As with all patients, clinicians should remain vigilant and responsive to potential known antibiotic-associated adverse drug events (ADEs) that may occur in pregnant women.

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TABLE 2 Summary of antibiotic safety recommendations in pregnancy.

Antibiotics	Prior pregnancy category	Notes (updated PLLR labeling)
Aminoglycosides		
Amikacin, gentamicin, streptomycin, tobramycin, and plazomicin	D	Reports of total, irreversible, bilateral congenital deafness have been associated with streptomycin All aminoglycosides carry a boxed warning for risk of fetal harm with use during pregnancy, with the highest risk during the first trimester Generally avoided in pregnancy Short-term use of aminoglycosides (excluding streptomycin) is acceptable with monitoring, if benefits outweigh the risks Topical aminoglycoside preparations are considered safe for use in pregnancy
Penicillins		
Penicillin, ampicillin, amoxicillin, and pivmecillinam	B	Generally safe to use
Cephalosporins (all generations) and cephamycins		
Ceftriaxone, ceftolozane, cefiderocol, and ceftobiprole	B	Generally safe to use Ceftriaxone should be used with caution at term due to concern of kernicterus in the neonate
Beta-lactamase inhibitors		
Clavulanic acid, tazobactam, sulbactam, avibactam, vaborbactam, durlobactam, and enmetazobactam	B	Generally safe to use
Carbapenems		
Ertapenem, meropenem, imipenem, and sulopenem (with probenecid)	B	Generally safe to use Sulopenem/probenecid should only be used when benefits outweigh the risks
Fluoroquinolones		
Ciprofloxacin, levofloxacin, moxifloxacin, and delafloxacin	C	Avoid in pregnancy due to renal toxicity, cardiac defects, and CNS toxicity in the fetus May use if there are no alternatives
Glycopeptides		
Vancomycin	B	Generally safe to use
Lipoglycopeptides		
Telavancin, oritavancin, and dalbavancin	C	Telavancin carries a boxed warning for fetal risk and should be avoided Oritavancin and dalbavancin may be used if the benefit outweighs the risk but are generally avoided in pregnancy due to class-wide effects
Lipopeptides		
Daptomycin	B	Generally safe to use
Macrolides and fidaxomicin		
Erythromycin, azithromycin, clarithromycin, telithromycin, and roxithromycin	B/C	Should be used with extreme caution as multiple studies have demonstrated risk of spontaneous abortion and major birth defects
Fidaxomicin	B	Limited data. May be used if benefit outweighs the risk
Oxazolidinones		
Linezolid and tedizolid	C	May use if the benefit outweighs the risk
Rifamycins		
Rifapentine, rifampin, rifabutin, rifaximin, and rifamycin	C	Rifampin, rifamycin, and rifapentine are generally safe to use Caution should be used with rifabutin and rifaximin due to limited data

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TABLE 2 (Continued)

Antibiotics	Prior pregnancy category	Notes (updated PLLR labeling)
Tetracyclines and Glycylcyclines		
Doxycycline, minocycline, tetracycline, eravacycline, tigecycline, and omadacycline	D	Avoid due to proven teratogenicity May use if the benefit outweighs the risk (e.g., tick-borne illnesses)
Miscellaneous antibiotics		
Clindamycin	B	Generally safe to use
Fosfomycin	B	Safe and effective in the first trimester Limited data in second and third trimesters
Lefamulin	N/A	May cause fetal harm based on animal studies and should be avoided
Metronidazole	B	Topical metronidazole is safe to use in pregnancy Avoid systemic use in the first trimester Generally safe to use with caution in second and third trimesters
Nitrofurantoin	B	Safe to use in the first trimester Avoid in patients at or near term and in neonates under 1 month of age
Polymyxin B and E	C	May be used with extreme caution if benefit outweighs the risk
Pretomanid	N/A	Avoid due to lack of data
Sulfamethoxazole/Trimethoprim	D	Avoid unless the benefit outweighs the risk If SMX/TMP is first-line therapy regardless of pregnancy status (e.g., pneumocystis pneumonia), must supplement with 4 mg daily of folic acid

Abbreviations: CNS, central nervous system; PLLR, pregnancy and lactation labeling rule; N/A, not available based on year of approval; SMX/TMP, sulfamethoxazole/trimethoprim.

As with established BLIs, newer BLIs including vaborbactam, avibactam, durlobactam, and enmetazobactam are typically only studied in combination with beta-lactams, with pregnancy data derived mostly from animal studies. Vaborbactam, a non-beta-lactam boronic acid BLI, is co-formulated with meropenem and was FDA approved in 2017. Currently, there are no studies or case reports to date on the use of vaborbactam in pregnant patients, and the manufacturer's labeling does not include specific pregnancy-related warnings.[20] Avibactam, a non-beta-lactam serine BLI, is combined with ceftazidime and was FDA approved in 2015. In June 2023, a case report was published documenting the use of ceftazidime/avibactam during pregnancy. Ceftazidime/avibactam was used in a 23 + 5 weeks gestation patient with urosepsis and a past medical history of recurrent UTIs.[27] The cultures grew OXA-48 carbapenemase and CTX-M-2 extended spectrum beta-lactamase (ESBL) co-producing *Klebsiella pneumoniae*, susceptible to ceftazidime/avibactam. The patient received a 10-day course of ceftazidime/avibactam and was prescribed methenamine prophylaxis for the remainder of the pregnancy. The patient redeveloped urosepsis at 36 weeks and received an additional 10 days of ceftazidime/avibactam until she delivered the baby via a nonelective caesarean section at 37 + 3 weeks. The infant was born healthy without complications but developed symptoms of early-onset sepsis and was treated accordingly. The infant had no complications 2 months after discharge, suggesting the use of ceftazidime/avibactam during pregnancy did not cause any fetal harm, consistent with prior safety data of beta-lactams and BLIs.[27]

Durlobactam, a diazabicyclooctane BLI, is co-formulated with sulbactam. Animal studies of durlobactam (alone) showed increased skeletal variations of the hindlimb and asymmetrical ossification of the sternebrae and supernumerary ribs in mice when given subcutaneous doses of 2 and 4 times the maximum human dose.[20] These events were not found with intravenous administration.[20] Combination sulbactam/durlobactam was FDA approved in 2023 for the treatment of HAP and VAP due to *Acinetobacter baumannii*. Pregnancy was excluded in approval studies, and there are no available studies or case reports to date regarding its use during pregnancy. Per the manufacturer's label, there are no available data to evaluate for safety in pregnant patients with the combination.[20] Enmetazobactam, co-formulated with cefepime, is a penicillanic acid sulfone BLI that was FDA approved in 2024. Per the manufacturer's labeling, there are no available data as of this review on the drug-associated risk in those who are pregnant.[20] Similar to their beta-lactam counterparts, BLIs are considered to be generally safe for use in pregnancy.

3.4 | Fluoroquinolones

No additional published data regarding the safety of fluoroquinolone use in pregnancy was discovered by the authors, although a fourth-generation fluoroquinolone, delafloxacin, was approved in 2017. It is generally well accepted that all systemic fluoroquinolones should be avoided in pregnant patients due to the suggested association with

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renal toxicity, cardiac defects, and central nervous system toxicity in the fetus.[16] There are also animal data showing bone and cartilage damage to the fetus, but this is disputed among researchers.[16] Fluoroquinolones should only be used in pregnancy if there are no alternatives, and the benefit must outweigh the risk.

3.5 | Glycopeptides, lipoglycopeptides, and lipopeptides

No new data has emerged for the safety of vancomycin use during pregnancy since the previous review. Vancomycin is thought to be safe to use for the treatment of serious gram-positive infections, particularly in the second or third trimester.[16] However, new data in humans has emerged for long-acting lipoglycopeptides. A published case report of a 27-year-old pregnant woman (unknown pregnancy timeline) with methicillin-resistant *Staphylococcus aureus* tricuspid valve endocarditis was treated with four doses of once-weekly dalbavancin beginning on week 4 of total antibiotic therapy.[28] The patient gave birth on day 25 of dalbavancin treatment (day 52 overall) having received a cumulative dose of 2000 mg without adverse events noted in the pregnant woman or neonate.[28] Animal data for dalbavancin and oritavancin showed no fetal toxicity at clinically relevant doses.[20] Dalbavancin exposure at 3.5 times the MRHD resulted in delayed fetal maturation and increased fetal loss.[20] Oritavancin given to animals at doses equivalent to 25% of the single clinical dose of 1200 mg in humans showed no harm to the fetus. Higher doses were not evaluated in reproductive toxicology studies.[20] Dalbavancin and oritavancin should be used with caution in pregnant women until more post-marketing data become available.

Telavancin, a lipoglycopeptide with limited use in the United States, contains a boxed warning for fetal risk.[20] It is recommended that women have a serum pregnancy test prior to treatment with telavancin. This decision is based on three animal studies that administered clinically relevant doses of telavancin to rats, rabbits, and minipigs that raised concern for limb and skeletal malformations and fetal weight loss.[20] Telavancin should be avoided in pregnancy based on current data available, and other lipoglycopeptides should be used with caution due to class-wide effects.

The lipopeptide daptomycin is generally considered safe to use in pregnancy, bolstered by several published case reports.[29–33] In the published cases, pregnant patients received daptomycin 4–6 mg/kg, ranging from 14 to 42 days in duration. Daptomycin exposure in three of the cases was primarily during the third trimester, while two of the cases reported exposure primarily during the second trimester. No adverse events were noted in the pregnant women or newborns in the cases that provided complete data.[29–33] Many experts and clinical practice guidelines recommend higher doses of daptomycin (e.g., 8–12 mg/kg) than listed in the manufacturer's labeling to treat invasive *S. aureus* and *Enterococcus faecium* infections.[34,35] In the published cases to date, all pregnant patients received daptomycin 6 mg/kg or less, with the majority being dosed on total body weight. Among the cases with reported patient weight and daptomycin dose, three patients received 500 mg or less, and one patient received 800 mg (4 mg/kg).[30–33] In pregnant patients, careful consideration of optimal weight-based dosing should be used due to the potential for numerically higher ADEs when >8–10 mg/kg are given.[36]

3.6 | Macrolides and fidaxomicin

Since 2015, there have been additional studies demonstrating conflicting safety results of macrolide use in pregnant women. A 2017 study conducted by researchers from Quebec showed an increased risk of spontaneous abortion with exposure to macrolides during the first trimester.[37] There was a larger increase in spontaneous abortion in patients treated with clarithromycin (aOR = 2.35, 95% CI [1.90–2.91]) than in those treated with azithromycin (aOR = 1.65, 95% CI [1.34–2.02]). Findings were insignificant for those treated with erythromycin.[37] In a UK study comparing erythromycin, clarithromycin, and azithromycin to penicillin, macrolides demonstrated a significantly increased risk of any major birth defects and cardiovascular malformations compared to the use of penicillin antibiotics during pregnancy.[38] This study recommended that clinicians use alternative antibiotics in pregnancy. In response to the UK study, a Danish study was published that did not support the findings of an increased risk of major birth defects with the use of any macrolides (macrolides available in Denmark: azithromycin, clarithromycin, erythromycin, roxithromycin, and spiramycin) in pregnancy.[39] With these conflicting data and inconclusive agreement among scholars and clinicians, macrolide antibiotics (excluding fidaxomicin) should be used with extreme caution, considering studies have demonstrated a potential risk of spontaneous abortion and major birth defects.

Animal studies of intravenous fidaxomicin in rats and rabbits have shown that no embryo/fetal effects were noted at 66 to 245 times the clinically relevant dose.[20] However, in a phase 3 clinical trial, a participant with B-cell lymphoma received oral fidaxomicin along with methotrexate and vincristine. She became known to be pregnant on day 25 of study enrollment. The patient had a multiple-birth pregnancy and delivered three live and one dead fetus. Additionally, one live female fetus had a cleft palate.[40] Although limited, available data, along with the low overall oral bioavailability, suggest that fidaxomicin may be appropriate to use in pregnancy where benefits outweigh risks.

3.7 | Oxazolidinones

New data are available for the use of linezolid, specifically in use for *Mycobacterium tuberculosis* infections. In a study among pregnant patients with multidrug/rifampin-resistant tuberculosis, 27 patients had linezolid maternal drug exposure and 20 fetuses had fetal drug exposure at guideline-recommended doses.[41] The safety outcomes monitored in the study included preterm birth, miscarriage, stillbirth, termination of pregnancy, or low birth weight. The

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unadjusted OR was 0.68, 95% CI (0.25–1.82), $p = 0.447$, demonstrating no additional risk of linezolid as part of their tuberculosis regimen, although the study was not powered for this specific outcome.[41] Additionally, a case report of a 39-year-old pregnant woman with drug-resistant tuberculosis who received linezolid in the last 3 weeks of pregnancy did not show any fetal or maternal harm.[42] Tedizolid has no new data regarding safety in pregnancy, although there does not appear to be a reason for variability when compared to linezolid.[20] Based on the available evidence, oxazolidinones may be used in pregnant patients if the benefit outweighs the risk, considering more safety data exist in other agents used for gram-positive infections (e.g., vancomycin).

3.8 | Rifamycins

The rifamycin drug class includes the agents rifapentine, rifampin, rifabutin, rifaximin, and rifamycin. Rifapentine was shown to be teratogenic in animal studies; however, new data have emerged regarding its use in pregnant patients.[20] Safety outcomes among pregnant women ($n = 50$) and infants ($n = 49$) were evaluated in a study of once-weekly rifapentine plus isoniazid for tuberculosis prevention prescribed during the second and third trimesters.[43] Five mothers and six infants experienced a serious adverse event during the study; however, the authors concluded none of these events were related to rifapentine.

An expert review, including 442 women and 446 pregnancies, analyzed 109 women who were exposed to rifampin during the first trimester. The authors concluded that there was no increase in congenital abnormalities observed in infants born to mothers exposed to rifampin during the first trimester.[44,45] Of note, one of the studies analyzed reported an increased rate of fetal malformation of 4.4%, compared to the median rate of 1.8%, while other studies reported a rate of malformations less common than expected when on rifampin.[45] When administered in the final weeks of pregnancy, rifampin was shown to have an increased risk of maternal postpartum hemorrhage and bleeding in the exposed infant. Due to the increased risk of hemorrhage and bleeding, it is recommended to monitor the clotting parameters for patients who are on rifamycins and consider prophylactic vitamin K if the patient is being treated for tuberculosis.[46]

For rifabutin, there is a lack of human data to inform safety.[20] In animal studies, rats and rabbits were given doses up to 40 times the MRHD. In rats, rifabutin 200 mg/kg/day showed a decrease in fetal viability. At eight times the MRHD, rats showed an increase in fetal skeletal variants. At 16 times the MRHD, rabbits showed maternotoxicity and an increase in fetal skeletal anomalies.[20] Rifaximin, although approved for traveler's diarrhea, is most commonly prescribed for management of hepatic encephalopathy. If considered for antimicrobial use, it should be used with caution in humans due to teratogenic effects in animals.[20] Rifamycin was approved in November 2018 for the treatment of travelers' diarrhea caused by noninvasive strains of *Escherichia coli*. Rifamycin has negligible systemic exposure following oral administration and is not expected to result in fetal exposure to the drug.[20] Currently, there are no reports of use in pregnant patients. Embryofetal toxicity studies in rats and rabbits did not show malformations at 25,000 and 500 times greater plasma exposure based on area under the curve (AUC).[20] At 500 times the plasma exposure in rabbits, slightly higher incidences of fetuses with skull suture bone variations, enlarged skull fontanelle, and completely ossified digit 5 medial phalanx of both forelimbs, were observed.[20]

Based on available clinical data, rifapentine shows favorable data for safe use in pregnancy with continued vigilance due to the fetal adverse effects documented in animal studies. Rifampin is generally safe to use in pregnancy, although vigilance with monitoring and potential adjunctive management is needed. Data on rifabutin are limited and should be used with caution in pregnancy. Rifaximin has no available safety data in pregnancy and should be used with caution due to teratogenic events seen in animals. Rifamycin should be considered safe to use due to its minimal systemic and fetal exposure.

3.9 | Tetracyclines and glycylcyclines

Tetracyclines have proven teratogenicity in humans, and no new data are available on agents approved prior to 2015. Eravacycline and omadacycline, a novel fluorocycline and aminomethylcycline, respectively, were approved in 2018 for IAIs (eravacycline) and CABP and SSTIs (omadacycline). Animal studies of eravacycline showed an increase in postimplantation loss, reduced fetal body weights, and delays in skeletal ossification in rats and rabbits.[20] Omadacycline had similar animal study results, with proven placental crossing as well as delayed skeletal ossification of the developing fetus.[20] Although data are limited, eravacycline and omadacycline would be expected to have similar concerns with potential teratogenicity. Tigecycline is a glycylcycline antibiotic. In animal studies, it was shown to cross the placenta and was found in fetal tissues.[20] In rats and rabbits, tigecycline was associated with slight reductions in fetal weight and an increased incidence of minor skeletal anomalies at exposures of five times and one time the human daily dose based on the AUC, respectively. At human-equivalent maternotoxic doses, it was shown that an incidence of fetal loss was observed. Animal studies with rats have also shown that permanent discoloration of the teeth may occur when tigecycline is given during fetal tooth development. Tetracyclines and glycylcyclines should be avoided in pregnancy and only used when no alternatives are available, and benefit outweighs the risk. A clinical example of clear benefit of the use of tetracyclines is the management of certain tick-borne illnesses, where doxycycline is the drug of choice regardless of patient characteristics.[47]

3.10 | Miscellaneous antibiotics

3.10.1 | Clindamycin

In 2017, Celerity Pharmaceuticals LLC released an updated PLLR medication label for clindamycin.[48] A randomized controlled trial

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among 272 pregnant women in the second or third trimester examined the effects of 6 weeks of oral clindamycin, erythromycin, or placebo on birth weights and congenital malformations. Exposure to clindamycin did not impact rates of congenital malformations or birth weights when compared to those receiving placebo.[49] The updated label also included reference to a critical review on the topic which notes that in mothers who were given prescriptions for clindamycin in the first trimester, major congenital malformations were observed in 31 of 647 infants (4.8%) while the "expected rate" was 4.3%.[50] No congenital malformation was observed in the 16 infants born to women who took clindamycin during the first trimester for prevention of recurrent miscarriage. Among the 104 women who were treated with clindamycin in their second or third trimester, there was no documentation of an increase in the rate of major congenital malformations. Furthermore, 65 infants who were born to women who received clindamycin and quinidine for the treatment of malaria reported no increase in rates of congenital malformations.[50] The medication label update summarized that no clinical studies have reported findings of any potential risk of major congenital malformation or miscarriages. Therefore, clindamycin should generally be considered safe in pregnancy.[48]

3.10.2 | Fosfomycin

New data have emerged on the use of fosfomycin in pregnancy. In 2023, a large French study investigated pregnancy outcomes with the use of fosfomycin in the first trimester.[51] In the study, the fosfomycin group had a rate of 2.0% of major congenital anomalies, while the unexposed group had a rate of 2.1% (aOR = 0.97, 95% CI [0.73–1.30], $p = 0.86$).[51] The study concluded that congenital abnormalities were not associated with fosfomycin use during the first trimester. Additionally, a study conducted in Germany reported similar results, concluding that fosfomycin does not increase the risk of major congenital abnormalities when used in the first trimester of pregnancy.[52] Although data are limited on use after the first trimester, fosfomycin is generally considered safe for use in pregnancy.

3.10.3 | Lefamulin

Lefamulin is a pleuromutilin antibiotic approved by the FDA in 2019 for CABP.[20] Animal studies have demonstrated that lefamulin crosses the placenta and is found in fetal tissues. Studies in rats and rabbits have shown an increased incidence of postimplantation fetal and stillbirths at mean maternal exposures 0.4 times the mean exposure in clinical patients treated with lefamulin.[20] In these studies, the fetal bodies of these animals had decreased body weight, decreased ossification, and an apparent delay in sexual maturation, which have been a result of treatment-related development delay. It was also noted that malformations in rats occurred at systemic exposures greater than 40% of the average exposure in patients with CABP, which may indicate a risk for embryo-fetal toxicity. In humans, lefamulin is metabolized to 2R-hydroxy-lefamulin, which was noted to lead to an enlarged ventricular heart chamber in rats.[20] The manufacturer's labeling recommends assessing the pregnancy status of females of reproductive age prior to starting lefamulin and recommends the use of effective contraception during treatment and for 2 days after the final dose.[20] Additionally, there is a pharmacovigilance program for patients given lefamulin who are pregnant or become pregnant during therapy.[53] Overall, animal data suggest that lefamulin may cause fetal harm when administered to pregnant women and should be avoided.

3.10.4 | Metronidazole

Additional data on metronidazole were identified since our 2015 review article. The first was an expert review that concluded topical use of metronidazole for rosacea is safe for pregnant patients in all trimesters.[54] A case–control study by Muanda et al. showed that oral metronidazole should be avoided in the first trimester due to a 70% increased risk of spontaneous abortion.[37] These findings aligned with a previous Medicaid cohort study that showed a 67% increased risk of spontaneous abortion with metronidazole use.[37] Outside of the first trimester, metronidazole is generally considered safe, although caution should be used during the second and third trimesters.[54]

3.10.5 | Nitrofurantoin

In the same French study evaluating fosfomycin use during pregnancy, researchers also analyzed nitrofurantoin use in the first trimester.[51] The study showed a 2.5% incidence of major congenital abnormalities with nitrofurantoin as compared to 2.1% in the unexposed group. When nitrofurantoin was compared to fosfomycin, it was not associated with an increased risk of major congenital anomalies (nitrofurantoin, 2.5% vs fosfomycin, 2.0%; aOR = 0.80, 95% CI [0.44–1.47]). However, nitrofurantoin is contraindicated in pregnant patients at term, during labor and delivery, or when the onset of labor is imminent due to the risk of hemolytic anemia. Additionally, nitrofurantoin is contraindicated in neonates under 1 month of age due to concerns about hemolytic anemia. Nitrofurantoin is generally safe to use during the first trimester but should be avoided in pregnant patients at or near term and in neonates under 1 month of age.

3.10.6 | Polymyxin B and E

When evaluating data since the prior review, no new data have emerged for the use of systemic polymyxin B and E.[16] Given additional approvals of agents with activity against multidrug-resistant gram-negative infections, the use of polymyxin therapy is generally considered a last line and often avoided completely. Based on previous data of concerns with escalated toxicity in pregnant mice

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and anticipated high risk of adverse events in pregnant women, extreme caution should be exercised when using polymyxin therapy in pregnancy.

3.10.7 | Pretomanid

Pretomanid is an antimycobacterial nitroimidazole that was FDA-approved in 2019 for the treatment of multidrug-resistant tuberculosis. Currently, there is a lack of data regarding the use of pretomanid in pregnant women; however, embryotoxicity has been observed in animal studies.[20] In rats, doses equivalent to four times the human dose of 200 mg on an AUC basis showed increased postimplantation loss in the presence of maternal toxicity. In rabbits, there was no evidence of developmental adverse events. A pre- and postnatal developmental study using pregnant rats showed no adverse developmental effects in pups at doses up to 20 mg/kg/day from gestational day through lactation day 20. However, pups of pregnant females dosed at 60 mg/kg/day (about two times the exposure of the 200-mg dose in humans) showed lower birth weights and a slight delay in developing their airdrop righting reflex. This occurred at a maternally toxic dose. The use of pretomanid during pregnancy is currently not recommended in the World Health Organization 2020 tuberculosis guidelines due to a lack of studies in the pregnancy population.[55]

3.10.8 | Sulfamethoxazole-trimethoprim

No additional data are available on the use of sulfamethoxazole/trimethoprim in pregnancy. Based on historical data, the use of sulfamethoxazole/trimethoprim is cautioned in pregnant women. In clinical situations where sulfamethoxazole/trimethoprim is considered first-line therapy regardless of pregnancy (e.g., pneumocystis pneumonia), it is recommended to supplement with at least 4 mg/day of folic acid in pregnant patients receiving sulfamethoxazole/trimethoprim in their first trimester to reduce the risk of neural tube and other birth defects.[56]

4 | CONCLUSIONS

The use of antibiotics in pregnancy requires a multidisciplinary approach that includes a discussion of risk versus benefit to the pregnant woman and fetus. In many cases, bacterial eradication is imperative for the woman's safety as well as the proper development of the fetus. Many antibiotic classes are considered to be safe, including beta-lactams, fosfomycin, and clindamycin. However, certain antibiotics and drug classes should be avoided in pregnancy, such as telavancin, lefamulin, and tetracyclines. Among these antibiotics, telavancin requires a negative pregnancy test prior to therapy, and patients on lefamulin should be using effective contraception during treatment and for 2 days after the final dose. Continued post-marketing pharmacovigilance efforts with active scholarship of clinical outcomes in pregnancy are essential for expanding our understanding of antibiotic safety in pregnant patients, particularly with newly approved agents. By collecting and sharing data, health-care providers play a vital role in evidence-based guidance for safe antibiotic use in pregnancy.

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DATA AVAILABILITY STATEMENT

All data supporting the findings are reported within the article and/or supplementary materials.

ORCID

Johny Nguyen https://orcid.org/0009-0005-9196-8440
Christopher M. Bland https://orcid.org/0000-0001-8806-4583
Kayla R. Stover https://orcid.org/0000-0002-8635-0137
Lea S. Eiland https://orcid.org/0000-0001-7873-3157
Julia Keating https://orcid.org/0009-0006-9511-9072
Madeline Lemmon https://orcid.org/0009-0001-1560-8161
P. Brandon Bookstaver https://orcid.org/0000-0002-4409-0963

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